Research Proposal Form of the Thesis Entitled

Evaluation of Efficacy and Safety of Intranasal Dexmedetomidine and Intranasal Midazolam combined with Nitrous Oxide-Oxygen Inhalation Sedation in Management of Uncooperative Pediatric Dental Patients: A Randomized Cross-Over Clinical Study

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INTRODUCTION

Managing children's dental fear and anxiety (DFA) is a significant challenge for paediatric dentists. According to the Diagnostic and Statistics of Psychic Disorders DSM-IV, one of the most prevalent fears is dental fear, which is categorized as a specific fear. (Halonen et al., 2018) It frequently results in considerable unmet needs for dental treatment, which eventually deteriorate oral health. (Beaudette et al., 2017) Untreated dental conditions can result in pain and suffering, which can impair speech, eating, and learning. (Silegy & Jacks, 2003)

In order to treat most children efficiently and with little to no suffering, advanced equipment, meticulous patient management, behaviour modification or shaping, suitable local analgesia, and high technical skills can all be used. However, young children who are afraid or have particular needs find it difficult to handle stressful situations like dental appointments. In addition, children sometimes find it difficult to manage their fear, which might show itself as excessively crying or physically refusing, which makes it more difficult to provide them with the necessary dental care. The psychological anguish and distress caused by an unremarkable visit to the dentist may have a negative influence on the ability of parents and children to develop a healthy attitude towards oral health. (Sheta & Alsarheed, 2009) Other behavioural approaches to traditional non-pharmacological behavior treatment for such vulnerable children include hypnosis, relative analgesia, sedation, and general anesthesia (GA).

Hypnosis enables a person to focus on their inner experiences in an effort to change their thoughts, feelings, perceptions, and actions. However, the strategy only benefits motivated children who wish to learn and become proficient in it. (C. Wood & Bioy, 2008) The most common method for treating individuals who are reluctant or uncooperative is general anaesthesia. However, especially for small children, general anesthesia is not always recommended for dental care. This is due to the associated risks of morbidity and mortality, discomfort, the inconvenience of being without food by mouth for an extended period of time, and cost-effectiveness.(Bryan, 2002) Furthermore, the paradigm has changed in favor of safer conscious sedation techniques as a result of the U.S. Food and Drug Administration's warning against repeated or extended usage of general anesthetics and sedatives during treatments in children beneath the age of three due to their potential impact on developing brains. (*FDA Warnings Regarding Use of General Anesthetics and Sedation Drugs in Young Children and Pregnant Women | ACOG*, n.d.)

Mild sedation, or anxiolysis, is a medication-induced state in which cognitive and motor function may be affected without impairing any other reflexes and patients respond effectively to spoken instructions. A drug-induced condition of depression of consciousness known as moderate sedation, also known as conscious sedation, enables the patient to obey verbal directions, either on their own or in combination with light tactile stimulation. There is no need for measures to maintain a patent airway because spontaneous breathing is sufficient. Cardiovascular function is generally maintained. (Kapur & Kapur, 2018) Relative analgesia, also known as nitrous oxide–oxygen inhalation sedation, is a simple, secure technique that uses a nasal mask to deliver a mixture of oxygen (O2) and nitrous oxide (N2O) in various concentrations. It is well known for posing little to no risk, reducing anxiety, producing analgesia, and enhancing the ability of a patient and a healthcare professional to communicate effectively.("Practice Guidelines for Moderate Procedural Sedation and Analgesia 2018," 2018) Rapid absorption and excretion of nitrous oxide enables quick onset and recovery (two to three minutes). It protects the cough reflex while little affecting any other responses. (Holroyd, 2008) Nonetheless, some patients may find the sensation of losing control distressing, and claustrophobia sufferers may find the nasal hood uncomfortable and confining.(Khinda et al., 2023) Also the efficacy of nitrous oxide is hampered in children who are fearful, uncooperative and continuously crying. Premedication with sedatives can be used to address this anxiety.

A premedication can be delivered by oral, intranasal, intramuscular, intravenous, sublingual, transmucosal and inhalational routes. The oral route is the most widely used of these techniques because it doesn't irritate tissue or mucosa and has a good patient acceptance rate. Its primary disadvantages include, however, the drug's bioavailability, delayed onset, prolonged recovery, and inability to titrate. (Patel et al., 2018) Children's innate needle anxiety makes the intramuscular and intravenous routes less desirable, despite their considerable advantages for drug titration. The intranasal technique is thought to be a minimally invasive and effective replacement. The nasal mucosa has considerable vascularity, which contributes to its quick onset, simplicity, noninvasiveness, and high bioavailability.

A more recent generation of benzodiazepines, midazolam, has a large toxic/therapeutic ratio, a safety margin, and a quick onset and recovery, making it a popular choice for premedication. (Verma et al., 2012) However, paediatric patients' acceptance of it may differ

since it irritates the nasal mucosa. (Sheta et al., 2014) Similar to clonidine, dexmedetomidine is an imidazole molecule that agonistically binds to alpha-2 receptors. It is a relatively recent medication. The Food and Drug Administration approved its usage for short-term sedation of patients in the critical care unit in 1999. In 2008, its approved use was extended to include premedication for nonintubated patients before to and during surgical operations for sedation. It works quickly, lasts for a brief period, and keeps the airway open to allow for spontaneous breathing, which prevents hypoxia. Dexmedetomidine is a sedative that may be helpful for children since it has both analgesic and sedative properties. (Unkel et al., 2021).

STATEMENT OF PROBLEM

The existing body of published literature has primarily examined the effects of premedication with midazolam and dexmedetomidine in addition to general anaesthesia medications; however, its potential synergistic effects with nitrous oxide sedation have not been thoroughly investigated and have not taken into account the original purpose of this study.

CLINICAL IMPLICATION OF THE STUDY

A rapidly expanding field, paediatric dental sedation is an essential choice for treating children with anxiety that cannot be calmed down by traditional methods. For children who are recommended for dental general anaesthesia (DGA), the combined method of premedication with intranasal dexmedetomidine or midazolam and nitrous oxide oxygen inhalation conscious sedation can be a crucial substitute.

AIM

Primary Aim: To evaluate the efficacy of premedication with intranasal dexmedetomidine and intranasal midazolam on children’s acceptance of nasal mask and their overall behavior during pulpectomy following nitrous oxide oxygen inhalation sedation.

Secondary Aim: To assess the safety of the integrated sedation regimen by evaluating physiologic parameters in children.

OBJECTIVES

- To evaluate and compare sedation onset following premedication with intranasal dexmedetomidine and intranasal midazolam
- To assess and compare satisfactory mask acceptance by children following premedication with intranasal dexmedetomidine and intranasal midazolam
- To evaluate and compare depth of sedation following premedication with intranasal dexmedetomidine and intranasal midazolam combined with nitrous oxide oxygen sedation
- To evaluate overall behavior of children during pulpectomy procedure under the sedation regimen
- To assess and compare physiologic measures in both approaches, pre operative, intra operative and postoperative phases.
- To evaluate parents preference regarding sedation regimen used

PROPOSED HYPOTHESIS

When used as premedication in conjunction with nitrous oxide inhalation sedation, intranasal dexmedetomidine and intranasal midazolam will help with the mask acceptance satisfactorily and will improve the overall behavior of children thereby facilitating the treatment completion with ease along with maintaining the vital parameters within normal range.

NULL HYPOTHESIS

When used as premedication in conjunction with nitrous oxide inhalation sedation to manage apprehensive and fearful children undergoing dental treatments, there won't be a discernible difference in the efficacy and safety of intranasal midazolam and dexmedetomidine.

REVIEW OF LITERATURE

Background

Dental fear and anxiety are major barriers to providing children with high-quality care. Behavior control is a common issue for most children who get anxious before dental procedures. The frequency of dental anxiety and fear in children is reported to be between 5.7% and 19.5%. Children have been seen to have elevated levels of anxiety and noncompliance between the ages of three and seven, which diminishes with age. (Klingberg & Broberg, 2007). Avoidance of dental treatments due to anxiety is common and seems to be directly associated with a significant deterioration in oral and dental health, resulting in a vicious cycle of growing anxiety and avoidance. Dental anxiety and fear can generally be treated with psycho-therapeutic therapies, pharmaceutical interventions, or a mix of both, depending on the severity of the condition, the patient's characteristics, and the clinical conditions. (Appukuttan, 2016) The majority of children can handle the dental procedures with simple non-pharmacologic behavioral control techniques. However, these ideal circumstances aren't always achievable, necessitating the use of sedation and general anesthesia in pharmacologic management.(Wilson, 2004) Conscious sedation, when feasible, provides a safer alternative to general anesthesia, which has proven to be an effective method for practitioners to manage patients who are more susceptible. (Mourad et al., 2022)

Sedation in Pediatric Dentistry

The use of sedation is becoming more popular in paediatric dentistry since it makes the procedure relatively painless and contributes to the development of a favorable attitude towards dentistry. The two main categories of sedation are conscious and deep. But the new definition restricts the usage of the word "conscious sedation" to two levels: moderate sedation (formerly known as "conscious sedation") and light sedation (previously known as "anxiolysis"). (*Statement on Continuum of Depth of Sedation*, n.d.) When under conscious sedation, a patient is able to independently and persistently maintain a patent airway while also consciously responding to verbal commands, either on their own or in conjunction with mild tactile stimulation. (Kapur & Kapur, 2018). Recently, procedural sedation has been defined by the International Committee for the Advancement of Procedural Sedation as

follows: "the use of one or more medications to ease a diagnostic or therapeutic procedure while aimed a state during which hemodynamic stability, spontaneous respiration, airway patency, and protective airway reflexes are preserved, while alleviating pain and anxiety." (Gao & Wu, 2023)

Nitrous oxide-oxygen combination, midazolam, hydroxyzine, promethazine, ketamine, fentanyl, propofol, chloral hydrate, sevoflurane, and more recently, dexmedetomidine, melatonin, etc. are medication used for conscious sedation in paediatric dentistry. Worldwide acceptance of nitrous oxide inhalation sedation has grown as a result of its long history of safety and relatively few adverse effects. (Yee et al., 2019) However, it only works if the child breathes via their nose and accepts the nasal hood well, which is problematic for nervous or anxious children. Premedication is used to treat this anxiety before surgery, which makes the child more cooperative. It's not new; literature has long documented the usage of various pharmacologic drugs to maximize synergistic effects and minimize side effects by lowering individual doses. The length of the drug, its rate of metabolism, its pace of recovery, its excretion, and its side effects all influence the choice of sedative and how it is administered. (Gao & Wu, 2023; Mittal et al., 2015)

Children can be given sedative medications by oral, intramuscular, intravenous, intranasal, inhalational, or sublingual routes to help with anxiolysis and pain relief. Intravenous administration is the fastest way for a medication to take effect and the most effective way to titrate a drug to achieve the required blood concentration. However, continuous venous access need and the subsequent vein puncture that goes along with it is a significant drawback of IV administration, particularly when utilized for paediatric dental sedation. (Unkel et al., 2021) Since oral sedation is simple to administer, affordable, and does not need injections or cannula insertion, it is frequently preferred by both paediatric patients and dentists. Nevertheless, their concentration is significantly decreased as a result of hepatic first pass metabolism.(Silegy & Jacks, 2003) Compared to oral sedation, intranasal and inhalation sedation have the benefit of allowing direct drug absorption into the systemic circulation, which bypasses hepatic first-pass metabolism and results in increased bioavailability and a faster onset of effect. (Sheta et al., 2014)

Paediatric dentists usually combine many medications because the optimal sedative effects may not always be produced by a single pharmacological agent. By producing cumulative, mutually enhancing, and improved sedative effects, this poly-pharmacy approach enables

lower dosages of each individual medication. Furthermore, drugs can be combined to produce effects that are not possible with a single drug. (Nelson et al., 2022)

Nitrous oxide oxygen sedation

Nitrous oxide gas and oxygen are administered at a sub-anesthetic dosage for inhalation sedation. These gases, which are delivered via nasal mask, depress the central nervous system with little to no influence on the respiratory system, resulting in different degrees of analgesia and anxiolysis depending on the amount of gas provided. (Holroyd, 2008) Additionally, it makes unpleasant dental operations easier for the patient to tolerate by reducing or alleviating pain, discomfort, or anxiety. Furthermore, it improves response time and decreases pressure-related discomfort without changing pulpal sensitivity. (Grønbæk et al., 2014) Nitrous oxide is readily eliminated from the blood (2–3 minutes) as soon as the delivery is discontinued since it has low blood solubility. Malamed and Clark stated that a 30%–40% nitrous oxide–oxygen concentration is the optimal for sedation in children. When performed appropriately and with equipment that is kept up to date, the nitrous oxide-oxygen sedation has a very high success rate and minimal side effects.(Malamed & Clark, 2003) However, since a continuous supply of the sedative agent is needed during the procedure, employing inhalation medicines in patients who are reluctant to accept the nasal mask presents difficulties. If the patient is sobbing uncontrollably or is a mouth breather who cannot handle inhaling via the nasal hood, the inspired concentration of nitrous oxide would be decreased, hence diminishing effects. Premedication can be used to overcome this situation. (Becker & Rosenberg, 2008)

Midazolam Sedation in Pediatric Dentistry

A more recent generation of benzodiazepines, called midazolam, has a large toxic/therapeutic ratio and safety margin. It acts quickly and briefly and possesses anxiolytic, anticonvulsive, muscle relaxant, and amnesic properties. In paediatric dentistry, midazolam is a highly sought-after sedative agent. (Gentz et al., 2017) It functions by stimulating the γ-aminobutyric acid (GABA). Due to its lipophilic nature, midazolam has a quick onset, quick recovery, and a short half-life due to liver metabolism. Midazolam is mostly used in the treatment of paediatric patients for two purposes: for conscious sedation and as premedication to lessen anxiety before general anaesthesia is induced. Since injectables frequently cause children's anxiety, discomfort, and stress, parenteral delivery via intravenous or intramuscular methods is discouraged whenever feasible, especially for young patients. (Kupietzky & Houpt, n.d.)

Both the oral and rectal methods are commonly used to deliver midazolam; however, the oral route has a 40% bioavailability. (Verma et al., 2012) Oral midazolam has been shown to be an effective sedative medication for paediatric dentistry outpatients when given in doses ranging from 0.5 to 0.75 mg/kg of body weight prior to around 30 minutes of the procedure. (Alzahrani & Wyne, 2012) Because midazolam is absorbed quickly via the extremely vascular nasal mucosa, administering medication intranasally has become more common. The typical time to peak plasma concentrations for a dosage of 0.2–0.3 mg/kg is 10 min, and the duration of action is about 30 min.(Kupietzky & Houpt, n.d.) Nonetheless, there is a documented burning sensation on the nasal mucosa while using intranasal midazolam. The side effects of midazolam are essentially minimal. The negative consequences of high dosages of midazolam, which can be reversed with flumazenil, include hypoventilation, related hypoxemia, and paradoxical responses. (Gao & Wu, 2023)

Dexmedetomidine Sedation in Pediatric Dentistry

In 1999, the Food and Drug Administration approved dexmedetomidine, a strong central α2-adrenoceptor agonist with short half-life, for use in premedication and sedation of patients in intensive care units. In 2005, it was first used in dentistry. By acting on the Locus Ceruleus, Dexmedetomidine (DEX) causes drowsiness that is comparable to that of natural sleep.(Devasya & Sarpangala, 2015) Because DEX preserves spontaneous ventilation, sparing respiratory effects, and maintains upper airway tone, it is a preferred choice for moderate sedation in children, particularly those who are at risk of apnea, hypoventilation, or respiratory depression. Few studies have shown bradycardia and vasodilatation as a result of the drug's vagomimetic effects, which are induced by its significant affinity for α2-adrenoceptor receptors.(Gao & Wu, 2023) It is used to sedate children by the buccal, oral, or intranasal routes of administration. Dexmedetomidine has a bioavailability of approximately 82% following intranasal treatment; sublingual and intranasal delivery result in the highest absorption. For premedication, 1-2 μg/kg of intranasal dexmedetomidine should be administered 45 minutes to an hour prior to induction of anaesthesia, and 2-3 μg/kg/dose for procedural sedation, in paediatric patients aged 6 months to 18 years. Dextmedetomidine has half-lives of roughly six minutes in distribution and two hours in terminal elimination. It is appropriate for paediatric dental sedation due to its rapid onset and brief duration of effect. (Freriksen et al., 2022)

Studies with midazolam and/or dexmedetomidine for pemedication combined with nitrous oxide inhalation sedation for managing uncooperative pediatric dental patients.

The research supports up the use of several drugs in child management, noting that the combination approach can reduce side effects and increase children's cooperation by lowering the overall dosage of each drug.(Sivaramakrishnan & Sridharan, 2017) In order to evaluate the combined effects of midazolam, nitrous oxide, and oxygen sedation as a safe and effective alternative to DGA, Wood et al. carried out an experiment in 2010. 96% of the necessary dental work was finished satisfactorily, and the patients were determined to have maintained verbal communication, hemodynamic stability, and the absence of clinically significant oxygen desaturation throughout the process. (M. Wood, 2010) In a clinical trial, hemodynamic parameters, mask acceptance, and the onset of sedation were recorded until anaesthesia induction in children aged 3-6 years undergoing complete dental rehabilitation. Premedication with intranasal midazolam (0.2 mg/kg−1) and intranasal dexmedetomidine (1 μg/kg−1) was administered. When compared to midazolam, it was shown that intranasal dexmedetomidine induced better sedation, less postoperative agitation, and a longer onset of sedation. (Sheta et al., 2014) When intranasal midazolam (0.1 mg/kg body weight) is combined with nitrous oxide for dental treatment, it causes sedation and recovery more quickly than oral midazolam (0.2 mg/kg body weight), according to a research by Musani et al. on children aged 4 to 10. However, there was no discernible difference between the two regimens under study in terms of acceptance of the nasal mask, sedation score, crying intensity, motor movements, or overall behavior ratings.(I. E. Musani & Chandan, 2015). In 3-6 year old children receiving general anesthesia for dental treatment, Wang et al. found no significant differences in the acceptability of the mask or parental separation after oral midazolam (0.5 mg/kg body weight) and intranasal dexmedetomidine (2 μg/kg body weight) as premedication agents. In comparison to the MID group, the proportion of agitated children in the DEX group was much lower, and this difference was statistically significant. (Wang et al., 2020) The children's ability to effectively accept the nasal mask is crucial to the effectiveness of nitrous oxide inhalation sedation. Musani et al. conducted a study in 2021 on the premeditation of anxiety in children who are unwilling to accept it. According to the authors, children who were uncooperative during dental treatment responded well to a combination of nitrous gas and intranasal midazolam (0.1 mg/kg body weight). Midazolam was also found to be an effective premedication agent for anxiolysis. (I. Musani et al., 2021)

When oral midazolam or oral midazolam combined with oral hydroxyzine and nitrous oxide was compared to intranasal dexmedetomidine with nitrous oxide for moderate sedation during paediatric dental procedures, there was no statistically significant difference in effectiveness, according to a retrospective study conducted in 2021 by Unkel et al on children aged 3-6. But when stimulating and time-consuming operations were taken into account, the DEX sedation regimen performed better.(Unkel et al., 2021)

MATERIAL AND METHODOLOGY

Ethical consideration

Ethical approval for the study will be taken from the ethical committee of the institution prior to the start of the study. The subjects as well as parents will be explained about the whole procedure verbally and informed written consent will be obtained (English/Gujarati/Hindi) from the parent/legal guardian of each child who is going to participate in the study. All parents/ legal guardians and children will be given the option to refuse the treatment. Only patients and parents who will give the written informed consent will be included in this study.

Study Design: Crossover, Prospective, Triple blind, Randomized Clinical Study

Place of Study: Department of Pediatric and Preventive Dentistry, Karnavati School of Dentistry, Gandhinagar, Gujarat**.**

Source of data: Children who are accompanied by parents, guardian, caretaker or next to their kin reporting to the OPD of department of Pediatric and Preventive Dentistry, Karnavati School of Dentistry, Gandhinagar, Gujarat.

Sample size calculation :

The Sample size formula:

$n=(A+B)^2[p_1(1-p_1) + p_2(1-p_2)]/(p_1-p_2)^2$

n = minimum sample size required for two group

p_1 = first proportion = 0.72

p_2 = second proportion = 0.45

$p_1 – p_2$ = difference between clinical proportions = 0.27

A = desired significance level 5% = 1.96

B = desired power 80% = 0.84

n = 45 sample size

Total sample size for the study will be 45.

Selection Criteria

Inclusion Criteria

- Young uncooperative/ anxious, otherwise healthy children aged 4-7 years.
- Children of ASA Grade I according to American Society of Anesthesiologists (ASA, 2020)
- Patient who require pulp therapy in primary molars in both the mandibular quadrants
- Children with Frankel's behavior rating scale 1 and 2

Exclusion criteria

- Chronic obstructive pulmonary diseases
- Habitual mouth breather
- Specially abled children
- Depressed conscious level
- Current upper respiratory tract infections
- Recent middle ear disturbance/surgery
- Treatment with bleomycin sulfate, Cobalamin (vitamin B_{12}) deficiency
- Allergy to any drug used in the study
- Patients/ parents/ legal guardians who refuse to give consent

Randomization and Allocation

After recruiting the patients meeting inclusion criteria, the individuals will be randomized into two groups using digital allocation method. In Group A, patient will be premedicated with 0.1mg/kg intranasal midazolam followed by nitrous oxide inhalation sedation in first visit and premedication with intranasal 1 µg/kg dexmedetomidine followed by nitrous oxide oxygen inhalation sedation will be administered in second visit. In Group B, patients will be

premedicated first with dexmedetomidine followed by nitrous oxide sedation and on second visit premedication with midazolam followed by nitrous oxide sedation will be performed. A washout period of 14 days will be kept between two visits.

Materials and Equipment to be used:

❖Protective Barriers

- Surgical Gloves
- Mouth Mask
- Head Cap
- Protective EyeWear
- PPE kit

❖Set Of Diagnostic Instruments

- Mouth Mirror
- Dental Probe
- Dental Tweezer

❖Local Anesthesia Used

- Lignocaine Spray (Lidalyn®, lignocaine 15%w/v)
- 2% Lignocaine with Adrenaline 1:80,000 (Xicaine®, ICPA)
- Disposable Syringe (2ml) With 26 Gauge Needle (Unolok®)

❖Armamentarium and material for pulp therapy

❖ConSed analgesia machine (Consed International, Kerala, India)

❖Pulse oximeter (BPL Smart Oxy)

❖Multipara patient monitor

❖DEXIT 50 vial (Dexmedetomidine 50 mcg/ 0.5 ml, Troikaa Pharmaceuticals Ltd)

❖ Mezolam vial (Midazolam hydrochloride 5mg/ml, Neon Laboratories Ltd)

Clinical Procedure

The proposed study will be conducted as a cross over randomized clinical trial adhering to guidelines by Declaration of Helsinki. Before including the children in the trial, information sheet will be provided to the parents explaining the study procedure, risks, and advantages of the treatment. The anesthetist will assess general health of each patient prior to enrollment. The fasting protocol recommended by American Academy of Paediatric Dentistry's will be explained to the parents and followed. The dosage will be calculated depending on patient's weight. Baseline parameters such as oxygen saturation, heart rate and blood pressure will be recorded. Intranasal premedication will be administered by trained personal. The operator, the patient and the observer will be blinded to the premedication agent used. Washout period of 14 days will be kept between two appointments. All the procedures will be performed in all children by a single operator. Recording of various scales used for the study throughout the procedure will be performed by the same observer during the two visits and the vitals will be observed by anesthetist.

Intranasal Midazolam and Dexmedetomidine Administration

A dosage of 0.1mg/kg intranasal midazolam hydrochloride (Mezolam 5mg/ml, Neon Laboratories Ltd) and intranasal dexmedetomidine at 1 μg/kg (DEXIT, dexmedetomidine 50mcg/ 0.5ml, Troikaa Pharmaceuticals Ltd) will be administered to patient according to group allotted. The intranasal dexmedetomidine and midazolam will be prepared by the anesthetist according to the patient's body weight. Saline 0.9 % will be added to make a final volume of 1 ml. In the presence of one parent, equal volume of the drug will be sprayed into two nostrils with mucosal atomizer device with the child in a recumbent position in the pre-operative holding area by trained nurse. After every 5 minutes of administering the premedication drug, the onset of sedation will be scored. The vitals will also be recorded. The patient will be transferred to the operatory once sedated (glazed look, lack of muscle coordination, slurred speech) and one parent/guardian will be allowed to accompany.

Administration of Nitrous Oxide (N_2O)- Oxygen ($O_{2)}$ Inhalation Sedation

After making the patient sit on dental chair, the nasal hood will be introduced. After that, the appropriate size of nasal hood will be selected and fitted. The acceptance of nasal mask will

be recorded according to the Mask Acceptance Scale (MAS). (Akin et al., 2012) According to guidelines of AAPD, a flow rate of five to six liters per minute (L/min) generally is acceptable to most patients. (Chernik et al., 1990) ("American Academy of Pediatric Dentistry. Use of Nitrous Oxide for Pediatric Dental Patients. ," n.d.) Introduction of 100 percent oxygen will be done for one to two minutes. The percentage of N_2O will be started initially at 10%. Then, it will be titrated in approximately 10% increment rise every 60 s till 30% concentration. Local anesthesia will be given by standard procedure. Subjective and objective effectiveness of local anesthesia will be checked. Depth of sedation will be assessed during local anesthesia administration. Following this, the planned pulp therapy of teeth requiring about 40-45 minutes will be performed. The ease of completing the treatment will be recorded by evaluating overall behavior using Houpt's Ease of treatment completion scale. (Houpt et al., 1986) At the end of the procedure nitrous will be slowly reduced and 100% oxygen will be delivered for 5 minutes to prevent diffusion hypoxia. All patients will be expected to stay in the observatory for 30-45 minutes. The child will be discharged after assessing the vitals, response to verbal stimulation, state of wakefulness, and ability to walk unaided.

The next appointment for the patient will be scheduled after 14 days which is the washout period for study. The abovementioned protocol will be followed for each patient in both the groups.

ASSESSMENT OF PARAMETERS

Physiologic Parameters

Heart rate (HR) and Oxygen saturation (Spo2) will be recorded using pulse oxymeter and Blood pressure using digital sphygmomanometer at baseline, at onset of sedation, during nasal mask induction, intraoperatively during local anesthesia administration and postoperatively.

Onset of sedation

Onset of sedation will be recorded in minutes (Smith et al., 1998)

- Glazed appearance

- Delayed movement of eyes
- Muscle incoordination
- Slurred speech
- Sleepiness

The Acceptance of Nasal Mask

The acceptance of nasal mask for nitrous oxide inhalation sedation will be assessed using Mask Acceptance Scale. (Akin et al., 2012)

Clinical Picture	**Score**
Cooperative, not afraid, easy to accept the mask	1
Easy to comfort, slight fear of mask,	2
Difficult to calm through comfort, moderate fear of mask,	3
Crying or struggling, afraid,	4

Evaluation of sedation level The Sedation achieved following premedication and nitrous oxide inhalation will be evaluated using Modified Observer's Assessment of Alertness/Sedation Scale (Chernik et al., 1990)

Score	**Description**
6	Appears alert, awake and responds to name spoken in normal tone readily
5	Though appears asleep, responds to name spoken in normal tone readily
4	Responses lethargically to name spoken in normal tone
3	Only responds after name is called repeatedly or loudly
2	Only responds after mild prodding or shaking
1	No response to mild prodding or shaking
0	No response to noxious stimulus

Ease of completing the treatment

Ease of completing the pulp therapy procedure after local anesthesia administration under premedication and nitrous oxide sedation will be noted using Ease of Treatment Completion Scale. (Houpt et al., 1986)

1	Aborted; No treatment rendered
2	Poor; Treatment interrupted, only partial treatment completed
3	Fair; Treatment interrupted but eventually all completed
4	Good; Difficult, but all treatment performed
5	Very good; Some limited crying or movement
6	Excellent; No crying or movement

Parents' preference for sedation regimen

Parents' satisfaction regarding efficacy of paired sedation technique will be assessed as Good, fair or poor.

STATISTICAL ANALYSIS

After collection of data, the data will be entered in Microsoft Excel 2019. The data will be presented as proportions, mean ± standard deviation. The normality of the data will be checked and the parametric and non- parametric tests will be applied for comparison using SPSS version 23 at significance level $P<0.05$.

REFERENCES

AAPD | Guidelines for Monitoring and Management of Pediatric Patients Before, During, and After Sedation for Diagnostic and Therapeutic Procedures. (n.d.). Retrieved March 23, 2024, from https://www.aapd.org/research/oral-health-policies--recommendations/monitoring-and-management-of-pediatric-patients-before-during-and-after-sedation-for-diagnostic-and-therapeutic-procedures/

Akin, A., Bayram, A., Esmaoglu, A., Tosun, Z., Aksu, R., Altuntas, R., & Boyaci, A. (2012). Dexmedetomidine vs midazolam for premedication of pediatric patients undergoing anesthesia. *Paediatric Anaesthesia*, *22*(9), 871–876. https://doi.org/10.1111/j.1460-9592.2012.03802.x

Appukuttan, D. P. (2016). Strategies to manage patients with dental anxiety and dental phobia: Literature review. *Clinical, Cosmetic and Investigational Dentistry*, *8*, 35–50. https://doi.org/10.2147/CCIDE.S63626

Beaudette, J. R., Fritz, P. C., Sullivan, P. J., & Ward, W. E. (2017). Oral Health, Nutritional Choices, and Dental Fear and Anxiety. *Dentistry Journal*, *5*(1), 8. https://doi.org/10.3390/dj5010008

Becker, D. E., & Rosenberg, M. (2008). Nitrous oxide and the inhalation anesthetics. *Anesthesia Progress*, *55*(4), 124–130; quiz 131–132. https://doi.org/10.2344/0003-3006-55.4.124

Bryan, R. a. E. (2002). The success of inhalation sedation for comprehensive dental care within the Community Dental Service. *International Journal of Paediatric Dentistry*, *12*(6), 410–414. https://doi.org/10.1046/j.1365-263x.2002.00400.x

Chernik, D. A., Gillings, D., Laine, H., Hendler, J., Silver, J. M., Davidson, A. B., Schwam, E. M., & Siegel, J. L. (1990). Validity and reliability of the Observer's Assessment of Alertness/Sedation Scale: Study with intravenous midazolam. *Journal of Clinical Psychopharmacology*, *10*(4), 244–251.

Devasya, A., & Sarpangala, M. (2015). Dexmedetomidine: A Review of a Newer Sedative in Dentistry. *Journal of Clinical Pediatric Dentistry*, *39*(5), 401–409. https://doi.org/10.17796/1053-4628-39.5.401

FDA Warnings Regarding Use of General Anesthetics and Sedation Drugs in Young Children and Pregnant Women | ACOG. (n.d.). Retrieved January 28, 2024, from https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2016/12/fda-warnings-general-anesthetics-sedation-drugs-young-children-pregnant-women

Freriksen, J. J. M., van der Zanden, T. M., Holsappel, I. G. A., Molenbuur, B., & de Wildt, S. N. (2022). Best Evidence-Based Dosing Recommendations for Dexmedetomidine for Premedication and Procedural Sedation in Pediatrics: Outcome of a Risk-Benefit Analysis By the Dutch Pediatric Formulary. *Paediatric Drugs*, *24*(3), 247–257. https://doi.org/10.1007/s40272-022-00498-y

Gao, F., & Wu, Y. (2023). Procedural sedation in pediatric dentistry: A narrative review. *Frontiers in Medicine*, *10*. https://www.frontiersin.org/articles/10.3389/fmed.2023.1186823

Grønbæk, A. B., Svensson, P., Væth, M., Hansen, I., & Poulsen, S. (2014). A placebo-controlled, double-blind, crossover trial on analgesic effect of nitrous oxide-oxygen inhalation. *International Journal of Paediatric Dentistry*, *24*(1), 69–75. https://doi.org/10.1111/ipd.12027

Halonen, H., Nissinen, J., Lehtiniemi, H., Salo, T., Riipinen, P., & Miettunen, J. (2018). The Association Between Dental Anxiety And Psychiatric Disorders And Symptoms: A Systematic Review. *Clinical Practice and Epidemiology in Mental Health : CP & EMH*, *14*, 207–222. https://doi.org/10.2174/1745017901814010207

Holroyd, I. (2008). Conscious sedation in pediatric dentistry. A short review of the current UK guidelines and the technique of inhalational sedation with nitrous oxide. *Paediatric Anaesthesia*, *18*(1), 13–17. https://doi.org/10.1111/j.1460-9592.2007.02387.x

Houpt, M. I., Rosivack, R. G., Rozenfarb, N., Odont, & Koenigsberg, S. R. (1986). Effects of Nitrous Oxide on Chloral Hydrate Sedation of Young Children. *Anesthesia Progress*, *33*(6), 298–302.

Kapur, A., & Kapur, V. (2018). Conscious Sedation in Dentistry. *Annals of Maxillofacial Surgery*, *8*(2), 320–323. https://doi.org/10.4103/ams.ams_191_18

Khinda, V., Rao, D., & Sodhi, S. P. S. (2023). Nitrous Oxide Inhalation Sedation Rapid Analgesia in Dentistry: An Overview of Technique, Objectives, Indications, Advantages, Monitoring, and Safety Profile. *International Journal of Clinical Pediatric Dentistry*, *16*(1), 131–138. https://doi.org/10.5005/jp-journals-10005-1807

Kupietzky, A., & Houpt, Ms. I. (n.d.). *Midazolam:a reviewof its use for conscioussedationof children*.

Malamed, S. F., & Clark, M. S. (2003). Nitrous Oxide-Oxygen: A New Look at a Very Old Technique. *Journal of the California Dental Association*, *31*(5), 397–402. https://doi.org/10.1080/19424396.2003.12224182

Mittal, N., Goyal, A., Jain, K., & Gauba, K. (2015). Pediatric Dental Sedation Research: Where Do We Stand Today? *Journal of Clinical Pediatric Dentistry*, *39*(3), 284–291. https://doi.org/10.17796/1053-4628-39.3.284

Musani, I., Bhure, S., Choubey, S., Musani, S. I., & Surve, S. (2021). Intranasal Midazolam Premedication for Anxiolysis in Children Reluctant to Receive Nitrous Oxide Sedation via Nasal Hood: An In Vivo Randomized Control Trial. *International Journal of Clinical Pediatric Dentistry*, *14*(Suppl 2), S138–S142. https://doi.org/10.5005/jp-journals-10005-2092

Musani, I. E., & Chandan, N. V. (2015). A comparison of the sedative effect of oral versus nasal midazolam combined with nitrous oxide in uncooperative children. *European Archives of Paediatric Dentistry: Official Journal of the European Academy of Paediatric Dentistry*, *16*(5), 417–424. https://doi.org/10.1007/s40368-015-0187-7

Nelson, T., Wilson, S., & Tanbonliong, T. (2022). Opioid and Multi-Drug Pediatric Dental Sedation: A Narrative Review. *Journal of Dentistry for Children (Chicago, Ill.)*, *89*(1), 57–65.

Patel, V., Singh, N., Saksena, A. K., Singh, S., Sonkar, S. K., & Jolly, S. M. (2018). A comparative assessment of intranasal and oral dexmedetomidine for procedural sedation in pediatric dental patients. *Journal of Indian Society of Pedodontics and Preventive Dentistry*, *36*(4), 370. https://doi.org/10.4103/JISPPD.JISPPD_40_18

Practice Guidelines for Moderate Procedural Sedation and Analgesia 2018: A Report by the American Society of Anesthesiologists Task Force on Moderate Procedural Sedation and Analgesia, the American Association of Oral and Maxillofacial Surgeons, American College of Radiology, American Dental Association, American Society of Dentist Anesthesiologists, and Society of Interventional Radiology. (2018). *Anesthesiology*, *128*(3), 437–479. https://doi.org/10.1097/ALN.0000000000002043

Sheta, S. A., & Alsarheed, M. (2009). Oral midazolam premedication for children undergoing general anaesthesia for dental care. *International Journal of Pediatrics*, *2009*, 274380. https://doi.org/10.1155/2009/274380

Sheta, S. A., Al-Sarheed, M. A., & Abdelhalim, A. A. (2014). Intranasal dexmedetomidine vs midazolam for premedication in children undergoing complete dental rehabilitation: A double-blinded randomized controlled trial. *Paediatric Anaesthesia*, *24*(2), 181–189. https://doi.org/10.1111/pan.12287

Silegy, T., & Jacks, S. T. (2003). Pediatric oral conscious sedation. *Journal of the California Dental Association*, *31*(5), 413–418.

Sivaramakrishnan, G., & Sridharan, K. (2017). Nitrous Oxide and Midazolam Sedation: A Systematic Review and Meta-Analysis. *Anesthesia Progress*, *64*(2), 59–65. https://doi.org/10.2344/anpr-63-03-06

Smith, B. M., Cutilli, B. J., & Saunders, W. (1998). Oral midazolam: Pediatric conscious sedation. *Compendium of Continuing Education in Dentistry (Jamesburg, N.J.: 1995)*, *19*(6), 586–588, 590, 592.

Statement on Continuum of Depth of Sedation: Definition of General Anesthesia and Levels of Sedation/Analgesia. (n.d.). Retrieved January 31, 2024, from https://www.asahq.org/standards-and-practice-parameters/statement-on-continuum-of-depth-of-sedation-definition-of-general-anesthesia-and-levels-of-sedation-analgesia

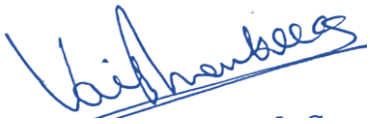
Unkel, J. H., Berry, E. J., Ko, B. L., Amarteifio, V., Piscitelli, W., Reinhartz, D., Reinhartz, J., & Warren, R. (2021). Effectiveness of Intranasal Dexmedetomidine with Nitrous Oxide Compared to Other Pediatric Dental Sedation Drug Regimens. *Pediatric Dentistry*, *43*(6), 457–462.

Verma, R. K., Paswan, A., De, A., & Gupta, S. (2012). Premedication with midazolam nasal spray: An alternative to oral midazolam in children. *Anesthesiology and Pain Medicine*, *1*(4), 248–251. https://doi.org/10.5812/aapm.4567

Wilson, S. (2004). Pharmacological Management of the Pediatric Dental Patient. *Pediatric Dentistry*.

Wood, C., & Bioy, A. (2008). Hypnosis and Pain in Children. *Journal of Pain and Symptom Management*, *35*(4), 437–446. https://doi.org/10.1016/j.jpainsymman.2007.05.009

Wood, M. (2010). The safety and efficacy of intranasal midazolam sedation combined with inhalation sedation with nitrous oxide and oxygen in paediatric dental patients as an alternative to general anaesthesia. *SAAD Digest*, *26*, 12–22.



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